DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 Dec 2009 has been entered.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 23 Dec 2009, in which claim 4 is are amended to change the phrasing of the claim and new claims 10 and 11 are added.

This application is the national stage entry of PCT/EP03/03183, filed 27 Mar 2003; and claims benefit of foreign priority document ITALY MI2002A00077, filed 11 Apr 2002. An English language translation of the foreign priority document is not currently of record.

Claims 1-11 are pending in the current application. Claims 2, 5 and 6, drawn to a nonelected species, are withdrawn. Claims 1, 3, 4 and 7-11 are examined on the merits herein.

Rejections Withdrawn

Applicant's Remarks, filed 23 Dec 2009, with respect to claims 1, 3, 4 and 7-8 rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of record) has been fully considered and is persuasive, as Applicant is persuasive that Jang et al. is drawn to the role of endogenous NO in arthritis and that the majority of data demonstrates negative effects of NO in cartilage matrix.

This rejection has been **withdrawn**. However, upon further consideration, a new grounds of rejection is made in view of Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Couchman et al. (Agents and Actions, 1986, 19(1/2), p116-122, cited in PTO-892) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of record) and Mariotto et al. (British J. Pharmacology, 1995, 115, p225-226, cited in PTO-892) as detailed below.

Applicant's Remarks, filed 23 Dec 2009, with respect to claim 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of record) as applied to claims 1, 3, 4 and 7-8 and further in view of Gabalawy et al. (Arthritis Res. 2002, 4 (suppl 3), pS297-S301, published 09 May 2002, of record) has

been fully considered and is persuasive, as Applicant is persuasive that Jang et al. is drawn to the role of endogenous NO in arthritis and that the majority of data demonstrates negative effects of NO in cartilage matrix.

This rejection has been **withdrawn**. However, upon further consideration, a new grounds of rejection is made in view of Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Couchman et al. (Agents and Actions, 1986, 19(1/2), p116-122, cited in PTO-892) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of record) and Mariotto et al. (British J. Pharmacology, 1995, 115, p225-226, cited in PTO-892) further in view of Gabalawy et al. (Arthritis Res. 2002, 4 (suppl 3), pS297-S301, published 09 May 2002, of record) as detailed below.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended Claims 1-3, 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Upon further review of the language of the claims, in claim 1 the term "the radical of a non steroidal anti-inflammatory precursor drug" (emphasis added) at line 12 and "the precursor drug" (emphasis added) at line 20 renders the claim indefinite. Claims 2,

3, 8 and 9 depend from claim 1 and incorporate all limitations therein. The ordinary definition of precursor in the biochemical and chemical arts is "A substance from which another is formed by a metabolic or other chemical process." (definition 3 of precursor, Oxford English Dictionary, cited in PTO-892). No limitation is given for what metabolic or other chemical process are required of the instantly claimed precursor. Therefore term "precursor" encompasses any possible chemical modification because any possible metabolic or other chemical process may be used to form it. Claim 1 recites administering an effective amount of one or more compounds or pharmaceutically acceptable salts of formula I. Lacking any structural requirements for said non steroidal anti-inflammatory precursor drug, it is unclear what amount is an effective amount of an unknown compound. Therefore, the term precursor drug renders the claims indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended Claims 1, 3, 4, 7-8, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Couchman et al. (Agents and Actions, 1986, 19(1/2), p116-122, cited in PTO-892) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of

record) and Mariotto et al. (British J. Pharmacology, 1995, 115, p225-226, cited in PTO-892).

Armour et al. discloses HTC1026 or flurbiprofen nitroxylbutylester (page 2185, left column, lines 10-11), the elected species, administered in vivo using a mouse model of ovariectomy-induced bone loss (page 2185, left column, lines 16-17). The Merck Index shows the structure of flurbiprofen (The Merck Index, of record). Armour et al. discloses flurbiprofen nitroxylbutylester may be used for treatment of rheumatoid arthritis, characterized by joint inflammation as well as periarticular and systemic bone loss (page 2185, right column, lines 8-12). Armour et al. discloses administration of flurbiprofen nitroxylbutylester by intraperitoneal injections in corn oil (page 2186, right column, lines 7-9), a method of parenteral administration. Armour et al. discloses HCT1026 retains the anti-inflammatory and analgesic activity of the nonnitrosylated parent compound, flurbiprofen, and that said compound is useful in inflammatory diseases such as rheumatoid arthritis (page 2192, left column, paragraph 1). Armour et al. teaches the administered HTC1026 retains its activity of inhibition of PGE_2 production (page 2187, right column, paragraph 1). Armour et al. teaches it is known in the prior art that there is cross-talk between the nitric oxide (NO) and PGE_2 pathways (page 2185, left column, paragraph 3).

Armour et al. does not specifically teach the method of treating degeneration of the cartilaginoid matrix comprising administering to a subject in need thereof an effective amount of one or more compounds or pharmaceutical salts thereof having the formula (I), or the elected species (instant claim 1).

Couchman et al. teaches it is known that NSAIDs significantly reduce cartilage degradation when incorporated into the synovial culture medium by action upon the production of chondrocyte stimulating factors (abstract). Couchman et al. teaches NSAIDs decrease the release of GAG, a measure of cartilage degradation, and appear to reduce the production of chondrocyte stimulating factors without affecting the action of chondrocyte stimulating factors similar to steroids (page 120, right column, paragraph 1).

Jang et al. teaches endogenous NO is known to play are role in arthritis (abstract) such as rheumatoid arthritis involving the cascade of events leading to loss of articular cartilage and resorption of bone (page 1511, left column, paragraph 1), and teaches in arthritis an increased loss of proteoglycans leads to cartilage dysfunction and eventually irreversible matrix degeneration (page 1515, right column, paragraph 1). Jang et al. teaches endogenous NO from chondrocytes can lead to both matrix degradation and proteoglycan synthesis and matrix synthesis, as well as PGE_2 leading to inflammation and matrix degradation (page 1515, Fig. 1 at top of page). Jang et al. teaches NO may play a chondroprotective role in cartilage matrix metabolism and limit proteoglycan degradation (page 1515, left column, paragraph 2). Jang et al. teaches it was observed that NO inhibition has elevated PGE_2 levels (page 1516, right column, paragraph 2), and that targeting both PGE_2 and NO by combination therapy may be an attractive intervention (page 1516, right column, paragraph 5).

Mariotto et al. teaches nitric oxide released from nitroflurbiprofen inhibits nitric oxide synthase (NOS) induction (abstract). Mariotto et al. teaches nitroflurbiprofen is

hydrolyzed *in vivo* to the NSAID flurbiprofen and NO, where the exogenous NO inhibits NOS induction (page 226, left column, paragraph 2). Mariotto et al. teaches the plasma NO^{2-}/NO^{3-} levels increase when either LPS or LPS+nitroflurbiprofen are administered while NOS activity decreases when LPS+nitroflurbiprofen is administered (page 226, table 1 at top of left column), implying that endogenous nitric oxide produced by NOS is reduced.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Armour et al. in view of Couchman et al. in view of Jang et al. and Mariotto et al. All of Armour et al., Couchman et al. and Jang et al. are drawn to the treatment of arthritis. One of ordinary skill in the art would be motivated to combine Armour et al. in view of Jang et al. because Jang et al. teaches targeting both PGE_2 and NO by combination therapy may be an attractive intervention, Armour et al. teaches an NSAID that inhibits PGE_2 production containing a NO donor moiety, and Mariotto et al. teaches the nitroflurbiprofen is known to be hydrolyzed *in vivo* to the NSAID flurbiprofen and NO. One of ordinary skill in the art would be motivated to select the patient population of subjects in need of treating degeneration of the cartilaginoid matrix because Couchman et al. teaches it is known that NSAIDs reduce cartilage degradation, Jang et al. teaches in arthritis an increased loss of proteoglycans leads to cartilage dysfunction and eventually irreversible matrix degeneration due to endogenous NO, and Mariotto et al. teaches nitroflurbiprofen provides exogenous NO that inhibits NOS induction implicitly reducing endogenous NO, suggesting treatment of that subpopulation of patients.

MPEP 2173.06 provides for the prior art rejection of claims containing terms that may be indefinite. In the instant case, the claims encompass "the radical of a non steroidal anti-inflammatory/analgesic drug" such as the elected species flurbiprofen.

Response to Applicant's Remarks:

Applicant's Remarks, filed 23 Dec 2009, have been fully considered and are not persuasive in view of the new grounds of rejection.

Applicant is persuasive that Jang et al. is drawn to the role of endogenous NO in arthritis and that the majority of data demonstrates negative effects of NO in cartilage matrix. However, in view of newly cited Mariotto et al., it appears the suggestion of Jang et al. of targeting both PGE_2 and NO by combination therapy implies the administration of exogenous NO in order to inhibit nitric oxide synthase (NOS) induction and thereby reduce endogenous NO as taught by Mariotto et al. The teaching of Jang et al. of negative effects of endogenous NO in cartilage matrix does not necessarily teach away from administering exogenous NO because of these different effects.

Amended Claims 1, 3, 4, 7-10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour et al. (Arthritis and Rheumatism, 2001, 44(9), p2185-2192, provided by applicant as reference AN in IDS filed 08 Oct 2004) in view of Couchman et al. (Agents and Actions, 1986, 19(1/2), p116-122, cited in PTO-892) in view of Jang et al. (Free Radical Biology & Medicine, 1998, 24(9), p1511-1519, of record) and Mariotto et al. (British J. Pharmacology, 1995, 115, p225-226, cited in PTO-

892) and further in view of Gabalawy et al. (Arthritis Res. 2002, 4 (suppl 3), pS297-S301, published 09 May 2002, of record).

Armour et al. in view of Couchman et al. in view of Jang et al. and Mariotto et al. teaches as above.

Armour et al. in view of Couchman et al. in view of Jang et al. and Mariotto et al. does not specifically teach the method wherein relapses of degeneration of the cartilaginoid matrix are reduced (instant claim 9).

Gabalawy et al. teaches relapse of rheumatoid arthritis is almost predictable after withdrawal of the antirheumatic drugs currently used in clinical practice (page S299, left column, paragraph 3). Gabalawy et al. teaches sustained or ongoing therapy may be used to reduce the possibility of a relapse (page S300, left column, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Armour et al. in view of Jang et al. and further in view of Gabalawy et al. Both Armour et al. and of Gabalawy et al. are drawn to drugs to treat rheumatoid arthritis. One of ordinary skill would have been motivated to combine Armour et al. in view of Jang et al. and further in view of Gabalawy et al. because Gabalawy et al. teaches antirheumatic drugs currently used in clinical practice can be applied in sustained or ongoing therapy to reduce the possibility of a relapse.

Response to Applicant's Remarks:

Applicant's Remarks, filed 23 Dec 2009, have been fully considered and are not persuasive in view of the new grounds of rejection.

Applicant's remarks with regard to Armour et al. in view of Jang et al. are addressed as above.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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